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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
FEB 81 M H WEEKS, M J TOPPER

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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM OF
CANDIDATE INSECT REPELLENT
AI3-20816-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY COMPOUND
STUDY NO. 75-51-0148-81
SEPTEMBER 1978 - NOVEMBER 1980

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-0148-81 (6)	2. GOVT ACCESSION NO. AD-A095	3. RECIPIENT'S CATALOG NUMBER 233
4. TITLE (and Subtitle) Topical Hazard Evaluation Program of Candidate Insect Repellent AI3-20816-a, US Department of Agriculture Proprietary Compound, Study No. 75-51-0148-81, September 1978- November 1980.		5. TYPE OF REPORT & PERIOD COVERED Final, Sep 78 - Nov 80
7. AUTHOR(s) 10) MAURICE H. WEEKS MICHAEL J. KOPPER, CPT, VC		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21210 0542		8. CONTRACT OR GRANT NUMBER(s) 9) Final rept.
11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Fort Sam Houston, TX 78234		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 11) 12 Feb 81 (12) 24/
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) (14) USAE HA-75-51-0148-81		12. REPORT DATE
		13. NUMBER OF PAGES 10
		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) USDA Proprietary Compound Eye irritation AI3-20816-a Photochemical irritation Topical Hazard Evaluation Sensitization Candidate repellent ALD Skin irritation		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hazard evaluation of candidate insect repellent AI3-20816-a was performed by means of laboratory studies using rats, rabbits, and guinea pigs. The technical grade compound causes mild skin irritation, but no eye irritation, no photochemical irritation in rabbits, no sensitization reaction in guinea pigs and did not demonstrate an acute ingestion hazard. However, 25 percent ethanol solutions of AI3-20816 cause moderate skin irritation reactions in rabbits. It is recommended that AI3-20816, USDA Proprietary compound be approved for further testing as a candidate insect repellent. Ethanol solutions may cause some skin		

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Item 20. Abstract. (continued)

irritation in sensitive individuals.

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Mr. Weeks/jc/AUTOVON
584-3980

11 FEB 1981

HSE-LT/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
AI3-20816-a, US Department of Agriculture Proprietary Compound,
Study No. 75-51-0148-81, September 1978 - November 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

A hazard evaluation of candidate insect repellent AI3-20816-a was performed by means of laboratory studies using rats, rabbits, and guinea pigs. The technical grade compound causes mild skin irritation, but no eye or photochemical irritation in rabbits, no sensitization reactions in guinea pigs, and did not demonstrate an acute ingestion hazard. Ethanol solutions of this compound caused moderate irritation of rabbit skin. It is recommended that AI3-20816-a, US Department of Agriculture Proprietary Compound, be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

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TOPICAL HAZARD EVALUATION PROGRAM OF
CANDIDATE INSECT REPELLENT
AI3-20816-a
US DEPARTMENT OF AGRICULTURE PROPRIETARY COMPOUND
STUDY NO. 75-51-0148-81
SEPTEMBER 1978 - NOVEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 13 September 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellent AI3-20816-a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent AI3-20816-a, US Department of Agriculture (USDA) Proprietary Compound, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study No. 75-51-0148-81, Sep 78 - Nov 80

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Slight erythema developed at 24 hours with skin appearing normal at 7 days. Details are shown in Appendix B.	USAEHA Category II (ref Appendix A)
0.5 mL technical grade compound applied to each of six rabbits.		
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL technical grade compound to one eye of each of six New Zealand White rabbits.	Small scattered areas of opacity in 3 of 6 rabbits at 24 hours. No signs at 48 hours, 72 hours, and 7 days. Details are shown in Appendix C.	USAEHA Category A (ref Appendix I)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u> Rats (male) - no diluent	ALD 6500 mg/Kg	Presents little lethal hazard from acute accidental ingestion.

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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single 0.05 mL application of a 25 percent (w/v) solution of each compound and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25 percent solution of AI3-20816-a in ethanol did not cause a photochemical irritation reaction under test conditions. Ethanol solutions of AI3-20816-a caused moderate erythematous and edematous reactions on both non-UV and UV skin sites.	Compound AI3-20816-a did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans.
<u>Control</u>		
Following UV exposures of the rabbits, 0.05 mL of test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48, and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas. Details are shown in Appendix D.	Ethanol solutions of this compound may cause moderate skin irritation in sensitive individuals. Persons experiencing this reaction should wash off the solution as soon as possible.

Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injection of 0.1 mL of a 0.1 percent solution (w/v) of AI3-20816-a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs for each compound were given 10 sensitizing doses over a 3-week period. After 2 weeks' rest, they were challenged with ID injections of each test compound.	Challenge dose of AI3-20816-a did not produce a sensitization reaction.	Compound AI3-20816-a did not produce a sensitization reaction under test conditions and is not expected to produce a sensitization reaction in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks' rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB produced a marked sensitization reaction in 10 out of 10 guinea pigs. Details are shown in Appendix E.	DNCB produced a marked reaction, indicating the guinea pigs respond to strong sensitizing agents.

* A known skin sensitizer.

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5. CONCLUSION. Technical grade compound AI3-20816-a caused mild skin irritation but no eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-20816-a be approved for further testing as a candidate insect repellent. Persons experiencing irritation when working with ethanol solutions of AI3-20816-a should wash the site with copious amounts of water.



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APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

APPENDIX B

COMPOUND: AI3-20816-a - USDA Proprietary Chemical				USAEHA STUDY NO. 51-0148-81					
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		TOXICITY CATEGORY USAEHA II		CONDITIONS - 0.5 mL technical grade compound applied under 2"x2" gauze patch for 24 hours.					
	Time of Observation (Hours)	Response Rabbit No.						Total Score	Comments
		477	478	479	480	481	482		
<u>Erythema & Eschar</u>									
Intact Skin	24 hr		2		2		1	5	
Intact Skin	72 hr		1		0		1	2	
Abraded Skin	24 hr	0		1		2		3	
Abraded Skin	72 hr	0		1		1		2	
						Subtotal		12	
<u>Edema Formulation</u>									
Intact Skin	24 hr		1		0		0	1	
Intact Skin	72 hr		0		0		0	0	
Abraded Skin	24 hr	0		0		1		1	
Abraded Skin	72 hr	0		0		0		0	
						Subtotal		2	
						Total		14	

APPENDIX C

COMPOUND: AI3-20816-a - USDA Proprietary Chemical										USAEHA STUDY NO. 51-0148-81									
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS					TOXICITY CATEGORY USAEHA A					CONDITIONS - 0.1 mL of compound instilled in conjunctival sac of right eye of each rabbit. No rinse.									
Time of Reading Hrs-Days	Structure	Scores								Mean Score	Comments								
		Rabbit No.																	
		459	460	461	462	463	464												
24	cornea iris conjunctivae	0	1	1	0	1	0	0	0.5										
		0	0	0	0	0	0	0	0.0										
		0	1	0	0	0	0	0	0.2										
48	cornea iris conjunctivae	0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										
72	cornea iris conjunctivae	0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										
7-days	cornea iris conjunctivae	0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										
		0	0	0	0	0	0	0	0.0										

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APPENDIX D

COMPOUND: A13-20816-a - USDA Proprietary Chemical USAEHA Study No. 51-0148-81

PHOTO CHEMICAL
IRRITATION
NEW ZEALAND WHITE
RABBITS

Comments: Moderately irritating in 95% ethyl alcohol
with or without UV exposure.

Observation Time	Mean Skin Irritation Score							
	Test Compound		Test Compound		Positive Control		Positive Control	
	UV Exposure	Edema	No UV Exposure	Erythema	UV Exposure	Edema	No UV exposure	Edema
24 Hours	2.0	2.5	1.8	2.0	2.0	1.0	1.5	0.7
48 Hours	2.0	2.3	1.8	2.0	1.5	0.8	0.0	0.0
72 Hours	2.0	2.5	1.8	2.0	1.3	0.7	0.0	0.0
Total Mean Irritant Responses	2.0	2.4	1.8	2.0	1.6	0.8	0.5	0.2

APPENDIX E

COMPOUND: AI3-20816-a - USDA Proprietary Chemical										USAEHA STUDY NO. 51-0148-81									
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN										<u>Substance:</u> Injected 0.1 mL ID of a .1% suspension of AI3-20816-a <u>Identify:</u> AI3-20816-a <u>Positive Control:</u> Dinitrochlorobenzene									
Scoring Time 24 hours		Mean Body Wt (G)		Mean Irritation Scores						Comments									
		Initial	Final	Diluent		Test Compound													
Test Compound		476 + 37	703 + 44	0.0	0.0	0.0	0.4	0.4	0.4	No sensitization potential demonstrated with test compound AI3-20816-a									
Positive Control		491 + 29	736 + 56	0.0	0.0	0.0	18	356											
Test Compd 48 hours		Mean Body Wt (G)		Mean Irritation Scores															
		Initial	Final	Diluent		Test Compound													
Test Compound		---	---	0	0	0	0	0	0										
Positive Control		---	---	0	0	0	5	272											
										Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing									